

Breakthrough Pain: Improving Recognition and Management to Enhance Quality of Life CME/CE

Complete author affiliations and disclosures are at the end of this activity.

Release Date: March 31, 2008; **Valid for credit through** March 31, 2009

Target Audience

This activity is intended for neurologists, family physicians, nurses, nurse practitioners, physician assistants, pharmacists, and specialists in anesthesiology, internal medicine, orthopaedics, rheumatology, psychiatry, and surgery who care for patients with chronic and breakthrough pain.

Goal

The goal of this activity is to improve recognition and management of breakthrough pain in patients with chronic pain.

Learning Objectives

Upon completion of this activity, participants will be able to:

1. Identify the challenges associated with evaluating breakthrough pain.
2. Recognize the impact that breakthrough pain has on morbidity and patient functioning.
3. Design individualized treatment plans for patients in order to optimize treatment outcomes.

Credits Available

Physicians - maximum of 1.25 *AMA PRA Category 1 Credit(s)*[™] for physicians;

Nurses - 1.25 nursing contact hours (0.75 contact hours are in the area of pharmacology);

Pharmacists - 1.25 ACPE continuing education credits for pharmacists (0.125 CEUs)

All other healthcare professionals completing continuing education credit for this activity will be issued a certificate of participation.

Physicians should only claim credit commensurate with the extent of their participation in the activity.

Accreditation Statements

For Physicians



Medscape, LLC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Medscape, LLC designates this educational activity for a maximum of 1.25 *AMA PRA Category 1 Credit(s)*[™]. Physicians should only claim credit commensurate with the extent of their participation in the activity.

For questions regarding the content of this activity, contact the accredited provider for this CME/CE activity: CME@medscape.net. For technical assistance, contact CME@webmd.net.

For Nurses

This Activity is sponsored by Medscape Continuing Education Provider Unit.

Medscape is an approved provider of continuing nursing education by the New York State Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation.

Awarded 1.25 contact hour(s) of continuing nursing education for RNs and APNs; 0.75 contact hours are in the area of pharmacology.

Provider Number: 6FDKKC-PRV-05

For questions regarding the content of this activity, contact the accredited provider for this CME/CE activity: CME@medscape.net. For technical assistance, contact CME@webmd.net.

For Pharmacists



Medscape is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Medscape designates this continuing education activity for 1.25 contact hour(s) (0.125 CEUs) (Universal Program Number 461-000-08-011-H01-P).

For questions regarding the content of this activity, contact the accredited provider for this CME/CE activity: CME@medscape.net. For technical assistance, contact CME@webmd.net.

Instructions for Participation and Credit

There are no fees for participating in or receiving credit for this online educational activity. For information on applicability and acceptance of continuing education credit for this activity, please consult your professional licensing board.

This activity is designed to be completed within the time designated on the title page; physicians should claim only those credits that reflect the time actually spent in the activity. To successfully earn credit, participants must complete the activity online during the valid credit period that is noted on the title page.

Follow these steps to earn CME/CE credit*:

1. Read the target audience, learning objectives, and author disclosures.
2. Study the educational content online or printed out.
3. Online, choose the best answer to each test question. To receive a certificate, you must receive a passing score as designated at the top of the test. Medscape encourages you to complete the Activity Evaluation to provide feedback for future programming.

You may now view or print the certificate from your CME/CE Tracker. You may print the certificate but you cannot alter it. Credits will be tallied in your CME/CE Tracker and archived for 6 years; at any point within this time period you can print out the tally as well as the certificates by accessing "Edit Your Profile" at the top of your Medscape homepage.

*The credit that you receive is based on your user profile.

This activity is supported by an independent educational grant from Cephalon.



Legal Disclaimer

The material presented here does not necessarily reflect the views of Medscape or companies that support educational programming on www.medscape.com. These materials may discuss therapeutic products that have not been approved by the US Food and Drug Administration and off-label uses of approved products. A qualified healthcare professional should be consulted before using any therapeutic product discussed. Readers should verify all information and data before treating patients or employing any therapies described in this educational activity.

Copyright © 2008 Medscape.

Contents of This CME/CE Activity

- Breakthrough Pain: Improving Recognition and Management to Enhance Quality of Life
Neal E. Slatkin, MD; Michelle I. Rhiner, RN, MSN, NP

Breakthrough Pain: Improving Recognition and Management to Enhance Quality of Life**Pre-Assessment: Measuring Educational Impact**[Skip Pre-Assessment »](#)

To help us assess the effectiveness of our medical education programs, please take a few moments to read the following cases and complete the questions that follow before participating in the CME activity.

Case #1: A 40-year-old man comes to your office complaining of chronic left wrist pain, which he has been experiencing ever since he fractured his wrist after slipping on some ice 3 years ago. He completed physical therapy and rehabilitation. Although his fracture healed and there is no radiologic evidence for malunion, he has constant pain in his left wrist, which he rates 5-6 out of 10. He also reports a worsening of his pain to 8 or 9 out of 10 once or twice during the day. On further questioning, you learn that the increase in pain intensity usually occurs at about the same times during the day, does not worsen with movement or upon lifting objects, and lasts between 30 and 45 minutes. Physical exam of the left wrist is inconclusive. He has been taking a long-acting opioid twice a day for his wrist pain for the past 11 months.

What is the most likely diagnosis?

- ☐ Idiopathic breakthrough pain (BTP)
- ☐ End-of-dose BTP
- ☐ Predictable incident BTP
- ☐ Unpredictable incident BTP

What would you do for management of this patient's BTP?

- ☐ Switch to another long-acting opioid
- ☐ Adjust the dosing of his current long-acting opioid
- ☐ Maintain him on the long-acting opioid and initiate a fast-acting opioid with a short duration of effect
- ☐ Add a second extended-release opioid to his current medication

Case #2: A 59-year-old man presents to your clinic for management of his pain. He was involved in a motorcycle accident 6 years ago in which he experienced injuries to his back and neck and has experienced intractable chronic pain in these areas since the accident. He uses a long-acting opioid (LAO) agent that mostly controls his pain.

In addition to his chronic back and neck pain, the patient describes an intermittent and severe stabbing pain in his lower back that prevents him from working and engaging in other activities of daily living. The pain occurs 4-5 times a day and lasts for at least half an hour. He rates the pain 8 out of 10. The stabbing pain usually follows daily activities such as walking for more than 4 blocks or climbing stairs. Physical exam is remarkable only for mild cervical joint tenderness.

What is the most likely diagnosis?

- ☐ Idiopathic BTP
- ☐ End-of-dose BTP
- ☐ Predictable incident BTP
- ☐ Unpredictable incident BTP

You recommend that he take rests between his activities and keep the activities as brief as possible. Which of the following would you choose to manage this patient's BTP?

- ☐ Tramadol
- ☐ Increasing the dose of the LAO agent
- ☐ A short-acting opioid in anticipation of the pain
- ☐ Switch to a different LAO of comparable or greater potency

Three months later, he reports recurring pain despite initial desired response following your appropriate management. What is your next step with this patient?

- ☐ Reassurance and wait to see if symptoms improve with more time
- ☐ Increasing the dose of the LAO agent
- ☐ Meditation and biofeedback classes
- ☐ Refer him to a pain specialist

Defining Breakthrough Pain

Breakthrough pain (BTP) may best be described as a transient exacerbation or flare of pain that occurs in patients with otherwise well-controlled baseline persistent pain.^[1] In as many as 85% to 90% of cases, BTP represents an exacerbation of the underlying persistent pain rather than an unrelated pain type; and in a small percentage of patients, more than one type may be present at a time. Several features, including the intensity, onset, and duration of the breakthrough episode, distinguish this pain subtype from the background persistent pain. Typically, the intensity of BTP is moderate to severe as pain is no longer controlled by the analgesic regimen being used to treat the persistent pain. Perhaps the feature that best distinguishes BTP is its abrupt onset, with the peak of pain severity occurring within 3-5 minutes from the time of onset. This rapid worsening typically contributes to the perceived severity of BTP, and can result in a patient quickly becoming immobilized by pain. Though for most patients the pain flare is fairly short-lived, resolving spontaneously in 30-90 minutes, it is not unusual for patients to have multiple episodes during the day that can cumulatively have a significant negative impact on overall patient comfort and quality of life (QOL).^[1-4]

According to a consensus panel for the assessment and management of BTP, the 3 subtypes of BTP are:

- ☐ Nociceptive, neuropathic, and visceral
- ☐ Incident (predictable or unpredictable), idiopathic (spontaneous), and end-of-dose
- ☐ Acute, chronic, and intermittent
- ☐ Mild, moderate, and severe

A consensus panel for the assessment and management of BTP has defined 3 subtypes: incident pain, idiopathic or spontaneous pain, and end-of-dose pain.^[1] Incident pain, which predictably occurs with activity or movement, is often relatively responsive to pharmacologic or other treatments, and comprises about 50% to 60% of cases of BTP. Some examples of conditions causing this pattern of BTP are vertebral and rib fractures of malignant or nonmalignant origin, where movement predictably causes an exacerbation of pain. With incident pain that is unpredictable, the relationship between pain and activity is more variable, with only certain types of activities or movements causing pain to flare. BTP arising from rib fractures may be triggered only by deep coughing or a particular pattern of truncal movement. As a result, it is far more difficult for the patient to reliably anticipate and successfully pretreat this type of BTP.

Idiopathic or spontaneous pain is not associated with any known precipitant and is perhaps less predictable in its duration and other characteristics than incident pain. Examples include colicky abdominal pain and true paroxysmal neuralgias. Although the duration of a single burst of pain may be relatively brief, repetitive bursts often characterize the painful episode, with only brief periods of respite between volleys of pain. The entire episode may last 30 to 90 minutes or longer and may be associated with a protracted period of suffering.

Pain exacerbations may also arise as the effect of a short- or long-acting medication used to control the persistent pain begins to wane just before the next scheduled dose is due, a condition known as end-of-dose pain. In such situations, the dose used to control the persistent pain may be inadequate or the dosing interval too long. End-of-dose pain generally has a more gradual onset and a longer duration than other types of BTP, especially if the background pain is being controlled by long-acting medications. In patients

experiencing end-of-dose pain, it is desirable to reassess and modify the around-the-clock analgesic regimen.

The reported prevalence of BTP in surveys of a variety of clinical populations has ranged from 16% to 95%.^[1,5-8] Because the original description of BTP was in cancer patients,^[7] it is not surprising that most of our prevalence figures are derived from that patient population. Two surveys of cancer inpatients conducted by Portenoy and colleagues^[7,9] have yielded prevalence rates of 50% and 65%. The prevalence of BTP in cancer outpatients is reported to range from 70% to 90%,^[4,10] and in hospice patients, regardless of whether pain was due to cancer or noncancer-related causes, it is almost 90%.^[2,11] In another study of 22 hospice patients, 86% (19 patients) experienced BTP, with an average of 2.9 episodes per day and a mean pain intensity of 7 on a 10-point scale, compared with an average daytime baseline pain score of 3.6 and an average nighttime baseline pain score of 2.6.^[2] The average duration of a BTP episode was 52 minutes (range, 1-240 minutes), and the average time to pain relief was 30 minutes (range, 5-60 minutes). This study also found that caregivers' perceptions of the patient's pain intensity, duration, amount of relief, and time to relief were likely to be inaccurate and were usually underestimated.

Finally, the diagnosis of BTP has been found to transcend national borders. An international survey of 1095 cancer patients showed an overall prevalence of nearly 65%, with higher reporting generally coming from English-speaking and European nations.^[6]

Although BTP has become widely recognized in noncancer patients, it is less often mentioned in the literature compared with cancer-related BTP.^[3] In patients with cancer, BTP is categorized by the disease state itself (cancer), regardless of where it occurs in the body or its pathogenesis. However, in noncancer patients, regulatory considerations have led to it being defined by the chronic pain condition with which it is associated (eg, neuropathic pain, low back pain, etc.). Subset analysis of a recent survey on noncancer-related BTP reported that 74% of patients received chronic opioids for low back pain and 78% of patients received chronic opioids for neuropathic BTP,^[12,13] percentages similar to BTP in the noncancer population as a whole.^[3]

Apart from differences in the clinical setting, the wide variability in the reported incidence of BTP may be attributed to the continuous changes in the definition of BTP over time. The definition of BTP (which has also been called "episodic pain" or "incidental pain") has been evolving over the years (see Table 1), and controversy over the best definition continues.^[6]

Table 1. Evolution of Definitions of BTP^[14]

Year	Definition
Portenoy, 1990 ^[7]	Transitory increase in pain to greater than moderate intensity, which occurs on a baseline pain of moderate intensity or less, in a patient receiving chronic opioid therapy*
Hanks, 1998 ^[15]	Transitory exacerbation of pain experienced by the patient who has relatively stable and adequately controlled baseline pain*
Coluzzi, 1998 ^[16]	Transitory flare of pain superimposed on an otherwise stable pain pattern in patients treated with opiates*
Bennett, 2005 ^[1]	Transient exacerbation of pain that occurs in patients with otherwise stable baseline persistent pain†
Abrahm, 2005 ^[17]	Moderate to excruciating acute pains that occur intermittently, often on a background of well-controlled chronic pain*
National Cancer Institute, 2005 ^[18]	Transitory increase in pain that occurs in addition to persistent pain*

*Definition based on cancer-related BTP

†Definition based on cancer- and noncancer-related BTP

Characteristics and Prevalence of BTP in Patients With Malignant and Nonmalignant Conditions

BTP often occurs in patients with cancer but, as previously indicated, can also occur in chronic disease patients with pain. The characteristics of BTP are similar in both groups of patients, and 1 or more common mechanisms may be involved.^[19,20] In a study of patients with controlled chronic noncancer baseline pain, 74% reported severe to excruciating BTP, with the most common syndrome being low back pain (52%).^[3] The median number of episodes per day was 2 (range, <1-12), and the median duration of BTP was 60 minutes (range, 1-720 minutes), characteristics similar to those of cancer patients. Therefore, any distinction between cancer and noncancer BTP may be arbitrary. This view is strengthened by the common occurrence of persistent and BTP in cancer survivors, whose pain is regarded as being cancer-related even though the chronicity and characteristics of the pain are typical of that experienced by chronic noncancer pain patients. For management, an understanding of the pain mechanism may therefore be more helpful than its differentiation as being of cancer or noncancer origin.^[21] Preliminary evidence indicates that regardless of whether a patient has a cancer-related or noncancer-related condition, their background pain may be worse if they have BTP.^[9]

Examples of BTP that is nociceptive in origin include all of the following *except*:

- ☐ Low back pain
- ☐ Bone metastases
- ☐ Osteoarthritis
- ☐ Chemo-neuropathy pain

As with chronic or persistent pain, BTP is also classified as being of nociceptive, visceral, or neuropathic origin. BTP that is nociceptive in origin arises from painful conditions of the bones, muscles, ligaments, and joints, examples being low back pain due to degenerative disc disease, bone metastases, or various rheumatologic conditions. Visceral pain is considered by some to be a subtype of nociceptive pain, whereas others believe that the physiology and neurochemistry of visceral pain is sufficiently different from other pain types as to place it in a separate category. Examples of conditions causing visceral BTP are liver metastases, partial obstructions of hollow viscera, and inflammatory bowel syndromes. BTP that is neuropathic in origin arises directly from a disease or dysfunction of the nervous system itself, such as postherpetic neuralgia and reflex sympathetic dystrophy.^[1,14]

Impact of BTP

Which pain scenario do you think would be more functionally disabling?

- ☐ Stable level of pain rated 3-4 on a 10-point scale with 4 episodes/day of BTP rated 7-8 on a 10-point scale in severity and lasting approximately 60 minutes
- ☐ Stable level of pain rated 5 on a 10-point scale with no episodes of BTP (ie, no exacerbations of pain > 6 on a 10-point scale)

Persons having persistent pain often experience a decrease in QOL, including a 4-fold greater likelihood of experiencing an anxiety or depressive disorder than do persons without persistent pain. The co-occurrence of BTP further additionally aggravates pain-related functional impairment and is itself associated with worse QOL. It has been observed that patients with BTP have more intense background pain than patients without BTP, as well as greater pain-related functional impairment, worse mood, and more anxiety.^[9] Another study showed that cancer patients with BTP had significantly higher "worst pain," with nonresponders to treatment having worse average pain, shorter time to "worst pain" severity, and higher Brief Pain Inventory interference parameters.^[4] Using a multivariate regression model, investigators found that worst pain severity most highly predicted the interference of pain with activities, and this in turn most predicted impairments in QOL. In chronic noncancer pain, the largest negative impacts of BTP on QOL have been found to be related to activity level and ability to work, with treatment having favorable effects on BTP and improving QOL.^[22]

BTP is associated with several other symptoms including derangements of sleep, increased hopelessness, and loss of interest in activities and relationships with others, leading to dissatisfaction with overall pain management (including opioid therapy) and worse medical outcomes.^[6,9,11,14,23] However, despite the impact of BTP on QOL measures, long-term controlled studies have not been mounted to assess the effects of BTP treatment in improving function, mood, and QOL.

Several studies have reported on the pharmacoeconomic impact of BTP. Overall, the occurrence of BTP appears to be associated with more pain-related hospitalizations, physician office visits, and higher economic costs.^[24-26] In one study of patients with cancer pain, the total cost of pain-related hospitalizations, emergency visits, and physician office visits was 12,000 US dollars per year per patient with BTP, as compared with 2400 US dollars per year per patient without BTP.^[24] Patients having BTP were 2 to 3 times as likely to be hospitalized or be seen in an emergency department as those having chronic pain without significant BTP episodes.

Recognition and Diagnosis of BTP

In your opinion, which category of barriers is the most significant with regard to the diagnosis of BTP? Select all that apply.

- ☐ Absence of a clear understanding of the definition of BTP on the part of healthcare providers
- ☐ Absence of a clear understanding of the definition of BTP on the part of patients
- ☐ Absence of a standardized assessment tool for BTP
- ☐ Absence of good outcomes studies showing the importance of recognizing and treating BTP

There is a general consensus among pain practitioners that BTP is often underdiagnosed and undertreated. Clinician-related factors (see Table 2) associated with underdiagnosis and undertreatment of BTP include lack of consensus on the definition of BTP, underrecognition of the occurrence of BTP in patients with persistent pain, inadequate knowledge of pain management, placing a low priority on pain management, and opioid-related concerns.^[14,18,27,28] The assessment of BTP has not been integrated into commonly used pain assessment tools such as the Brief Pain Inventory, thereby contributing to its underrecognition. Additionally, patients may have their own concerns and may be reluctant to report pain for fear of having higher doses of medication or additional medications prescribed that may cause adverse effects.^[29] The regulation of opioids, perceived professional liability risks, and problems with opioid availability are other barriers to effective treatment.^[18]

Table 2. Barriers to Effective Pain Management^[18]

Healthcare Professional-Related Barriers

- A. Inadequate knowledge
 - Pain assessment
 - Diversity of treatment approaches
 - Distinguishing characteristics of medications
 - Overestimation of opioid risks (eg, hypotension, respiratory depression, delirium)
- B. Regulatory and liability concerns
 - Concerns about prescribing controlled substances for specific pain states
 - Limitations on the amount of medication that can be prescribed
 - Concerns regarding abuse, addiction, and diversion
- C. Concerns regarding treatment
 - Efficacy
 - Side effects (eg, sedation, impairment of function, constipation, nausea, and emesis)
 - Tolerance
 - Addiction

Patient-Related Barriers

- Reluctance to report pain (eg, due to fear of pain medications, concerns about distracting healthcare providers from treating the underlying disease, concern about not being a "good" patient)
- Cultural and religious values and beliefs
- Cost of medications
- Concerns about the meaning of the pain (eg, concerns about disease worsening, disability)
- Fear of addiction or of being thought of as an addict
- Worries about increasing the side effects of pain medications, or interactions with other medications
- Concern that using more pain medications will lead to tolerance
- Reluctance to take pain medications and poor adherence with the prescribed analgesic regimen

Healthcare System-Related Barriers

- Low priority given to pain treatment
- Denial of medication coverage or inadequate reimbursement
- Most appropriate treatment may not be reimbursed or may be too costly
- Restrictive regulation of controlled substances
- Problems of availability of treatment or access to appropriate medications
- Opioids unavailable in the patient's pharmacy

Assessment

Please indicate your agreement with the following: When patients report on their "worst pain" during the day, they are usually describing an episode of pain that could be classified as BTP.

- ☐ Strongly agree
- ☐ Somewhat agree
- ☐ Neither agree nor disagree
- ☐ Somewhat disagree
- ☐ Strongly disagree

As with all subjective symptoms, the patient's verbal report serves as the best source of information on their experience of pain, and a careful questioning of the patient can contribute to a better understanding of factors that may provoke episodes of BTP. Asking patients their pain level from 0 to 10 without specifying such factors as the location of pain or whether the pain is their current, average, or worst pain is not likely to yield specific clinical information. Assessing BTP can be a challenge because commonly used screening tools such as the Brief Pain Inventory fail to include questions about BTP, and because patients are often unfamiliar with the term "breakthrough pain." Inquiring about the patient's "worst pain" may be a useful screening strategy, since typically a patient's "worst pain" represents an episode of BTP. Once the level of their "worst" pain has been established, follow-up questions can help to define the circumstances under which such pain occurs. If the patient's mental status is altered, such as by delirium or dementia, inferences about BTP may be made by noting the patient's nonverbal pain behaviors and the reports of caregivers.

It is important to assess and differentiate the pattern of BTP from the patient's persistent pain because the management of BTP differs from that of persistent pain. Details should be obtained about the location, severity, pattern, subtype, and temporal characteristics of the BTP. The character and location of BTP may suggest a nociceptive, neuropathic, or mixed etiology. This information, together with knowledge of the onset, intensity, and duration, will help in deciding on a management approach, including the choice of a pharmacologic agent and route of administration. Whenever possible, a correctable cause should be sought, using imaging studies when appropriate. Awareness of the specific impact of BTP on the patient's functional status and QOL will also help to determine the goals of treatment.^[1,14]

Which of the following do you use most often when assessing a patient for BTP?

- ☐ Visual Analog Scale
- ☐ Brief Pain Inventory
- ☐ The patient's pain diary
- ☐ All of the above
- ☐ None of the above

Several unidimensional and multidimensional tools can be used for pain assessment, but none have been fully validated for BTP. Unidimensional tools screen for pain severity only and are primarily used to establish the need for treatment and as a basis for initial medication titration as well as subsequent dose readjustment. Unidimensional tools include the commonly used Numeric Rating Scale, which involves rating pain on a scale of 0 to 10, and verbal descriptor scales rating pain along a continuum from "none" to "very severe." Although 1-dimensional scales provide no specific information about the characteristics of BTP, they are easy to use and are often relied upon to assess the response to treatment.^[1,14] Unidimensional tools include:

- **Numeric Rating Scale:** Patients rate their pain on a 0-to-10 scale or a 0-to-5 scale, with 0 representing "no pain at all" and 5 or 10 representing "the worst imaginable pain."
- **Visual Analog Scale:** The patient places a vertical mark at the level of their pain intensity along a horizontal 10-cm line. One end of the line is marked "no pain" and the other end is marked "the worst imaginable pain." The position of the mark is measured with a ruler to assign a score.
- **The Faces Pain Scale and the Wong-Baker Faces Rating Scale** have visual descriptors involving images of faces with various expressions (eg, smiling, frowning, grimacing, etc.), with the patient choosing the face that matches their own current level of pain. Such scales may be useful in young children and cognitively impaired adults but typically better convey the emotional significance of the pain (ie, its affective component) than its intensity.
- **Verbal Descriptor Scales.** These are nonlinear scales that use adjectives of pain severity to describe the intensity of the pain. The scales generally vary in the number of response options from 4 to 6 but always incorporate the terms "mild," "moderate," and "severe" among the verbal descriptors.

Multidimensional scales, such as the Brief Pain Inventory, characterize pain more thoroughly, having both quantitative and qualitative dimensions, but are time-consuming, often require input from a healthcare provider, and fail to specifically assess for BTP.^[1,14] Multidimensional tools include:

- Brief Pain Inventory: This tool quantifies pain intensity and the interference of pain with the patient's physical and emotional state of well being.
- McGill Pain Questionnaire: Pain is assessed in 3 dimensions (ie, sensory, affective, and evaluative) based on words that patients select to describe their pain.

A pain diary can be the most valuable source of information about a patient's baseline persistent pain as well as episodes of BTP. It can be used to collect multidimensional information and is designed for completion by the patient over the course of a day or longer. The pain diary is useful for initial evaluation and for ongoing monitoring, but a potential disadvantage is the time needed by the healthcare provider to interpret a large volume of information.^[1] The American Pain Foundation has developed a pain diary that is available online for download.^[30] A pain diary has been shown to be an appropriate way to assess the intensity of both persistent pain and BTP and is associated with high compliance, even in seriously ill patients. Patients who complete pain diaries often have a better understanding of their condition and ensuing treatment recommendations and feel empowered to better cope with their pain.^[31,32]

As patients begin treatment, and throughout their treatment course, periodic reassessment of their pain and treatment response is warranted. A popular mnemonic that was developed to assist clinicians in their continuing reassessment of patients is the "Four As." Although originally intended for use in patients receiving opioid analgesics, the need to periodically reassess analgesia, activities of daily living, adverse events, and aberrant drug-related behaviors may apply to any prescribed analgesic regimen.^[33]

BTP Management

What is the *most* desirable property of a BTP medication?

- ☐ Speed of pain relief
- ☐ Cost of the medication
- ☐ Ease of use
- ☐ Duration of pain relief
- ☐ Same compound as long-acting medication used in persistent pain

Managing BTP is often a challenging clinical problem. By definition, BTP is more severe than background persistent pain, typically evolves quickly, reaches maximal intensity within minutes, and then resolves within minutes to hours. Therefore, the goals of good BTP management are to develop and administer treatments that work rapidly to bring pain under control, but at the same time are brief enough in their effects so that after the episode of BTP has subsided, patients are not needlessly exposed to high levels of analgesics and their attendant risks of side effects.

Just as it is important to individualize the assessment and management of the patient's persistent pain, so too must the management of BTP be individualized. In patients with chronic pain, the treatment of BTP usually begins after the baseline persistent pain has been optimized and is stable. BTP is then independently assessed, with its cause and pattern determined through a detailed medical history, as described earlier. The analgesic regimen should then be adjusted and readjusted as needed by monitoring relevant treatment outcomes. Multidisciplinary regimens involving both pharmacologic and nonpharmacologic approaches may provide the best results.^[34]

Most patients with BTP can be managed successfully by their primary care provider. The clinician must identify and treat correctable causes of the pain. For example, if predictable incident pain occurs with a particular activity, the activity should be modified or avoided, or an appropriate analgesic should be taken prior to the activity in anticipation of the pain-provoking event. For end-of-dose pain, the management of baseline persistent pain should be reassessed, with higher doses or more frequent administration of the around-the-clock dose considered. Idiopathic and unpredictable incident pain is more difficult to treat because the onset of action and duration of effect of the analgesic agent employed may not coincide with the onset and duration of the pain. The dose and dosing frequency of around-the-clock drug therapy should be titrated to control persistent pain and also to minimize the occurrence of BTP, while maximizing the patient's activity level, alertness, and cognition.^[35,36]

Nonpharmacologic Approaches

Nonpharmacologic therapies for pain relief include application of cold or heat; use of braces, counter-irritant creams, or bandage

wraps; limitation of activity; correction of poor posture; reconditioning; exercise; massage therapy; transcutaneous electrical nerve stimulation (TENS); behavioral therapy; acupuncture; and nerve blocks.^[36,37] These approaches should be incorporated into the management strategy and integrated with pharmacologic therapy as needed. The management should be individualized using a multidisciplinary approach appropriate to each patient's pain profile.^[35]

Pain education programs involving basic principles of pain relief, pharmacologic interventions, and nondrug interventions for relief of pain have been shown to benefit both cancer patients and their family caregivers.^[31,38] Patients may require assistance in learning to recognize pain triggers and other techniques for managing BTP. For most chronic pain problems, complete pain relief is often not a realistic option, and an important goal of education lies in negotiating the patient's preferred balance between pain relief and side effects, and, in the process, establishing realistic expectations and goals for treatment. Patients need to be educated on the "yardsticks" used to measure improvements in pain control. While the perception of decreased pain is essential, enhancements in function and QOL are legitimate and quantitative outcome measures, which in some patients may precede a reported decrease in pain. Patients may also need to understand that although one of the goals of pain treatment is to allow for an increased level of activity, a "go slow" approach, with pacing of activities, may be important, especially during the early phases of reactivation. Some activities may be better tolerated when done in short segments rather than all at once. Anxiety and depression can interfere with the success of treatment, especially when it takes longer than anticipated to reach treatment goals, and counseling can be helpful for such patients.^[36]

Pharmacologic Therapy

By definition, BTP occurs on a background of otherwise stable, well-controlled baseline persistent pain. Although pharmacologic therapy for BTP starts with the effective management of the baseline persistent pain, specific management of BTP calls for "as-needed" or "rescue" doses of medications having a pharmacologic profile that matches the temporal pattern of the BTP as closely as possible.^[39]

Which one of the following classes of medication do you typically use first-line to manage BTP?

- ☐ NSAIDs, including acetaminophen
- ☐ Opioids
- ☐ Antiepileptics
- ☐ Antidepressants

Whenever feasible, it is best to manage predictable incident BTP with the preemptive use of a short-acting analgesic, usually an opioid, given prior to the scheduled activity or after the onset of pain, as quickly as possible. For end-of-dose BTP, the around-the-clock analgesic regimen should be modified by increasing the analgesic dose and/or shortening the dosing interval to better control baseline persistent pain. This may be done by increasing the total daily dose of the around-the-clock opioid by 25% to 50% and evaluating the response, or shortening the dosing interval if the patient is already taking the maximally tolerated dose. If a short-acting opioid is being used to treat the baseline persistent pain, conversion to a long-acting preparation should be initiated in order to minimize the chances that the BTP merely represents end-of-dose failure. Short-acting opioids may then be initiated for controlling the episodes of BTP occurring independently of the levels of the long-acting opioid.^[36]

The management of unpredictable or idiopathic BTP is particularly challenging because the pain reaches its peak intensity within 3-5 minutes of onset and lasts for about 30 minutes, whereas oral preparations may need 30 minutes or more for their onset of action. Therefore, a fast-acting analgesic medication with a relatively short duration of effect is needed to manage unpredictable episodes of BTP.^[39]

Choice of Pharmacologic Agent

Nonopioid analgesics, including acetaminophen, nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), and selective cyclooxygenase-2 (COX-2) inhibitors may be effective for managing BTP, but their use can be associated with dose-limiting toxicity; hence, they have a ceiling dose. Except for the treatment of headaches and joint pain, there is also no published evidence supporting the use of NSAIDs in BTP. Since the NSAIDs vary greatly as a class in their onset to analgesic effect, more rapid-acting agents such as acetylsalicylic acid, acetaminophen, and ibuprofen should be among the first agents chosen for a therapeutic trial. Other commonly used adjuvant analgesics, including those classified as antidepressants or anticonvulsants, likewise lack an evidence base in BTP treatment.^[36]

BTP is commonly treated with opioids.^[39,40] Unlike the NSAIDs, opioids do not have a predictable ceiling dose related to toxicity. This factor allows the dose of opioid to be titrated to optimal pain relief while minimizing side effects and without concern for hepatic, renal, cardiovascular, or other serious organ system toxicity. Since the majority of patients considered for opioid treatment for BTP are


already taking and tolerating long-acting opioids for persistent pain, side effects from the opioids added for BTP are seldom a major barrier to treatment. Although side effects, such as sedation, may initially hinder upward opioid dose titration, the majority of patients will become tolerant to these effects with continuing medication exposure, allowing titration to proceed, though perhaps at a slower rate. Occasionally, patients will have difficulty tolerating a particular opioid due to side effects, but with rotation to an alternative agent (eg, hydromorphone or fentanyl), the side-effect burden may be considerably lower.

Short-Acting vs Long-Acting Opioids

When initiating opioid therapy for persistent pain, treatment often begins with a short-acting opioid. The dosage is then gradually titrated to obtain optimum pain relief, balancing analgesia and side effects. Since combination opioids (ie, combinations with acetaminophen or another NSAID) have a ceiling dose imposed by the adjunctive agent, they are best avoided in this setting. Once the point of optimal analgesia is reached, the patient is switched to the equivalent dose of a long-acting formulation for around-the-clock dosing. For BTP, short-acting opioids are the primary treatment modality. The ideal BTP medication should have a short half-life to avoid accumulation if frequent dosing is needed, minimal or manageable adverse events, no interactions with the around-the-clock medication, and ease of administration.^[14]

The onset of opioid analgesia is largely determined by how quickly an opioid can gain access to the circulation and then to the pain-relieving areas of the brain and spinal cord. More lipophilic opioids, such as fentanyl, can rapidly move across the blood brain barrier (BBB), thereby quickly becoming available to the pain-modulating sites of the central nervous system. Even when hydrophilic agents such as morphine, oxycodone, and hydromorphone are injected intravenously, there is a significant time lag in their analgesic effect due to delayed transit across the BBB (Table 3). Fentanyl's high lipophilicity also allows it to be well-absorbed through the oral (buccal) mucosa, this route permitting earlier access to the circulation than orally administered opioid formulations that depend upon gastrointestinal absorption. These characteristics explain why transbuccal fentanyl formulations can have an earlier onset of effect and shorter duration of action than orally administered opioid formulations and why fentanyl is better suited than slower-acting agents for managing unpredictable incident BTP and idiopathic BTP.^[36]

Table 3. Characteristics of Immediate-Release Opioids Useful for BTP^[36]

 Hydrophilic	Immediate-release opioid	Onset of analgesia	Duration of effect	Remarks
	Morphine (oral)	30-40 minutes	4 hours	Slow onset of analgesia for idiopathic BTP
	Oxycodone (oral)	30 minutes	4 hours	Slow onset of analgesia for idiopathic BTP
	Hydromorphone (oral)	30 minutes	4 hours	Slow onset of analgesia for idiopathic BTP
	Methadone (oral)	~10-15 minutes	4-6 hours	Faster onset of analgesia seen in 1 small study; complex pharmacology
	Fentanyl (transmucosal)	~5-10 minutes	1-2 hours	Fastest onset of analgesia; requires ongoing patient cooperation in use
Lipophilic				

Since the opiate preparation used in the treatment of persistent pain is titrated to effect and given on a scheduled basis to maintain stable levels of analgesia, the efficacy of the medications used in persistent pain depends upon factors other than speed of onset. On the other hand, the very characteristics that define BTP, namely severity and rapidity of evolution, demand that opioids and opioid preparations used in treatment have a fast onset of effect and brief duration of action. Since the demands on therapy of persistent pain and BTP are so different, there is no requirement that the specific opioid used in treating one type of pain also be used in treating the other type. In other words, although it is perfectly reasonable to combine transbuccal fentanyl with transdermal fentanyl as respective treatments of both BTP and persistent pain, a different long-acting agent might reasonably be chosen instead of fentanyl for the persistent pain. The basic tenet of opioid therapy, namely independently titrating to efficacy both the long-acting and the short-acting agent, remains unchanged. The choice of an agent for BTP, therefore, should not depend upon the around-the-clock medication being used to treat persistent pain but upon the temporal characteristics of the BTP and the pharmacologic properties of the short-acting opioid.^[36]

Route of Administration

Because of the need for a rapid onset of analgesic action, a drug's route of administration is a major factor influencing the choice of BTP therapy.

Oral administration. Oral immediate-release formulations may be appropriate for predictable incident pain if given 30-45 minutes before the precipitating event, but their relatively slow onset of action makes them unsuitable for idiopathic or unpredictable incident BTP. If cost needs to be taken into account when choosing therapy, an oral immediate-release opioid may be a cost-effective choice.^[36] It is possible that some oral immediate-release formulations may have faster onset than others. A small study^[41] of oral methadone in cancer-related BTP found that some patients experienced relatively rapid onset of relief, a finding supported by another study only in comparison with oral morphine, not other short-acting opioids.^[42]

Oral transmucosal administration. As previously indicated, the oral transmucosal route of administration is well suited for delivery of fentanyl citrate due to its lipophilicity. The oral transmucosal delivery system incorporates fentanyl citrate in a matrix of sucrose fitted onto a plastic handle for dissolution within the oral cavity. Oral transmucosal fentanyl citrate (OTFC) is approved by the US Food and Drug Administration for use in cancer-related BTP.^[43] This formulation is an appropriate choice for patients with rapid-onset idiopathic or unpredictable incident BTP, especially if the pain significantly impairs activity or if it results in the patient seeking emergency medical care.^[36]

A randomized, double-blind, multicenter study compared OTFC and morphine sulfate immediate release (MSIR) for BTP in cancer patients receiving a fixed scheduled opioid regimen.^[44] Before entering the study, the patients were experiencing 1-4 episodes of BTP per day. OTFC was found to be more effective than MSIR, with scores of pain intensity and pain relief being significantly better with OTFC than MSIR ($P \leq .033$ and $P \leq .009$, respectively), and global performance of medication scores also favoring OTFC ($P < .001$). Another recent study examined the time to onset of meaningful pain relief for a variety of oral short-acting opioids and found OTFC clearly superior to all and rated as more effective by patients.^[42]

In a Cochrane review^[45] of studies involving opioids for managing BTP in patients with cancer, the evidence base was felt to support the use of OTFC as an effective treatment for BTP. OTFC was associated with lower pain intensity scores, higher pain relief scores, and better global assessment scores than morphine or placebo.^[45] Two other recent studies, not included in the Cochrane review, have likewise demonstrated the efficacy of OTFC in the treatment of BTP.^[46,47]

Buccal administration. The fentanyl buccal tablet (FBT) was specifically designed to enhance transbuccal absorption by inducing dynamic changes in the pH of the regional buccal mucosa.^[48] This new formulation is administered by placing a small tablet between the gum and cheek. In a randomized, double-blind, placebo-controlled study^[49] of opioid-tolerant patients with chronic cancer pain and BTP, FBTs demonstrated relief of BTP at 10 minutes, with an action that was sustained up to 2 hours postdose and was well tolerated.^[49] A randomized crossover study showed that the rate and extent of fentanyl absorption was greater following administration of FBTs compared with OTFC, and an approximately 30% smaller dose of FBTs achieved systemic exposures comparable to OTFC.^[50] Recent reports further suggest that sublingual administration of FBT results in a similar pharmacokinetic profile to transbuccal delivery, though further studies are necessary to validate this finding.^[51] Other advantages of FBTs over OTFC are a lesser need for patient education on administration of the formulation, a less conspicuous dosing method, and a lower risk of dental caries. Other transbuccal systems, such as those involving fentanyl in a bioerodible mucoadhesive matrix, are also under development. Small, uncontrolled studies have also suggested that methadone may be a useful compound for study via the sublingual route.^[52]

Sublingual and intranasal administration. Sublingual morphine has been used in patients with terminal cancer but has been associated with delayed absorption and attenuation and delay of peak morphine and metabolite levels.^[53] Buprenorphine and fentanyl are better absorbed sublingually than morphine.^[54] A sublingual fentanyl tablet being developed specifically for sublingual absorption dissolves rapidly and can produce detectable plasma drug levels in 8-11 minutes, with FBT also showing similar properties.^[51,55]

Parenteral administration. Parenteral opioids are widely used in inpatient (eg, postoperative) and hospice settings, but parenteral administration is costly and inconvenient in treating BTP in outpatients. However, parenteral opioid therapy, administered by patient-controlled administration devices in an outpatient setting, is often appropriate for the treatment of rapidly worsening pain in patients with advanced malignancies.^[56]

Patient-controlled transdermal delivery system. Transdermal fentanyl is employed for managing persistent pain. A patient-controlled iontophoretic transdermal system that provides on-demand systemic delivery of fentanyl has also been approved for the short-term management of acute postoperative pain in adult patients requiring opioid analgesia during hospitalization. With this system, the patient initiates a fixed fentanyl dose (40 mcg) by pressing a button twice within 3 seconds. An audible tone indicates the start of delivery of a dose, and a red light remains on during the 10-minute dosing interval. The next dose cannot begin until the previous delivery cycle has been completed. In a study comparing the fentanyl iontophoretic transdermal system with morphine intravenous patient-controlled analgesia, the 2 agents were found to be comparable for postoperative pain management.^[57]

Inhalation. The administration of opioids via the pulmonary route can be expected to be associated with a rapid onset of action if the

delivery system used is effective in distributing medication to the peripheral lung. A number of small investigations using a variety of delivery systems have therefore been performed to examine this route as a means for treating postoperative pain and BTP. Preliminary evidence, largely drawn from trials of nebulized opioids in dyspnea, has found pulmonary delivery to be safe, even in severely ill patients.^[55,58] A number of specialized systems have been shown to facilitate the delivery of inhaled opioids such as morphine and fentanyl in managing severe pain. Using one such system, the pulmonary delivery of morphine in approximately 3 micron-sized particles was shown to reduce cancer-related pain intensity more rapidly than oral morphine sulfate.^[59] New systems for pulmonary delivery of fentanyl are in the early phases of clinical development.^[60]

Rectal administration. The rectal route of administration is an option for a number of opioids including morphine, oxymorphone, and hydromorphone, but limitations of rectal administration include inconvenience, caregiver and personal sensitivities, broad variability in absorption, and a slower onset of action than that needed for managing BTP.^[36]

Intranasal administration. Morphine, sufentanil, and fentanyl have been administered intranasally, primarily in the postoperative or acute care setting, but further investigation into these delivery systems for the treatment of BTP is required before acceptance of their use into daily clinical practice.^[36]

Dosage

Please indicate your agreement with the following: The dose of a BTP medication should ordinarily be a fixed percentage (eg, 10% to 20%) of the total daily persistent pain medication dose.

- ☐ Strongly agree
- ☐ Somewhat agree
- ☐ Neither agree nor disagree
- ☐ Somewhat disagree
- ☐ Strongly disagree

Various guidelines have suggested that the dose of opioid for BTP should be in the range of 5% to 17% of the total daily opioid dose.^[36] However, there is little, if any, evidence base to support such an approach. Controlled studies with both morphine and transmucosal fentanyl indicate that the optimal dose for BTP cannot be predicted by the around-the-clock dose of opioids but must instead be found by titration.^[61,62] The cause, onset, severity, and duration of BTP varies from patient to patient, as does the patient's tolerance to opioids; therefore, dosage titration is carried out in an individualized manner similar to that employed for baseline persistent pain.^[36] Once the appropriate dose has been determined, there is usually no need to increase the dose of the BTP medication if the underlying disease condition is not progressive.^[46] Tolerance to the effects of BTP medication has not been reported as a common clinical problem.

The subtype of BTP also governs the dosing schedule. For end-of-dose pain, the dose and the administration of the around-the-clock medication need to be reevaluated. For predictable incident pain, a hydrophilic immediate-release opioid such as morphine or oxycodone can be given 30-45 minutes prior to the anticipated activity. For BTP that interferes with sleep, an opioid dose may be administered at night, or the dose of the controlled-release oral medication may be increased at night. In situations warranting an agent with a quicker onset and shorter duration of analgesia, OTFC or FBT can be considered. Transmucosal fentanyl is also an appropriate choice for unpredictable BTP having an onset of a few minutes and a short duration. For unpredictable BTP that has a slower onset or longer duration, an oral immediate-release hydrophilic opioid, or alternatively an NSAID, such as acetylsalicylic acid or ibuprofen, may be acceptable.^[36]

As with the use of opioids in the treatment of chronic persistent pain, the use of opioids in the management of BTP involves legal and regulatory considerations that must be rigorously attended to by prescribers. Practitioners must therefore thoroughly assess and monitor the patient, employ accepted principles of prescribing, and maintain proper documentation that supports the continuing need for treatment and benefits appreciated (eg, decrease in pain and improvement in function).^[36]

Referral to a Pain Specialist

BTP can generally be managed by the primary care clinician. Referral to a pain specialist may be considered in situations involving dose-limiting opioid toxicity, pain that is poorly controlled with immediate-release opioids, aberrant drug behavior of the patient, and patients requiring assessment for interventional pain techniques.^[36]

Post-Assessment: Measuring Educational Impact

Thank you for participating in the CME activity. Please take a few moments to read the following cases and complete the questions that follow to help us assess the effectiveness of this medical education activity.

In your experience, which of the following is the most important barrier you encounter to the optimal management of breakthrough pain (BTP)?

- ☐ Regulatory and liability concerns
- ☐ Concerns about efficacy and adverse effects of analgesic medications
- ☐ Low priority for pain management among healthcare professionals
- ☐ Underrecognition of the occurrence of BTP in patients with persistent pain

How confident are you that you are up to date in the diagnosis and management of BTP?

- ☐ Not at all confident
- ☐ Somewhat confident
- ☐ Confident
- ☐ Very confident

Case #1: A 58-year-old woman comes to your office for an evaluation of right shoulder pain. She has been experiencing chronic pain ever since she fractured her shoulder in a biking accident 2 years ago. She completed physical therapy and rehabilitation. Although her fracture healed and there is no radiologic evidence for malunion, she has constant pain in her right shoulder that she rates 5 out of 10. She also reports a worsening of her pain to 9 out of 10 once or twice during the day. On further questioning, you learn that the increase in pain intensity usually occurs at about the same times during the day, does not worsen with shoulder motions or carrying objects, and lasts almost 45 minutes. Physical exam of the right shoulder is inconclusive. She has been taking a long-acting opioid twice a day for her shoulder pain for the past 9 months.

What is the most likely diagnosis?

- ☐ Idiopathic BTP
- ☐ End-of-dose BTP
- ☐ Predictable incident BTP
- ☐ Unpredictable incident BTP

What would you do for management of this patient's BTP?

- ☐ Switch to another long-acting opioid
- ☐ Adjust the dosing of her current long-acting opioid
- ☐ Maintain her on the long-acting opioid and initiate a fast-acting opioid with a short duration of effect
- ☐ Add a second extended-release opioid to her current medication

Case #2: A 52-year-old woman presents to your clinic for management of her pain. She was involved in a car accident 4 years ago that required multiple surgeries for pelvic fracture and bladder rupture and has experienced intractable chronic pelvic pain ever since. She uses a long-acting opioid (LAO) agent that mostly controls her pain. In addition to her chronic pain, the patient describes an intermittent and severe stabbing pain in her lower back and pelvic girdle that prevents her from keeping up with daily routines. The pain occurs 4-5 times a day and lasts for half an hour. She rates the pain 8 out of 10. The stabbing pain usually follows daily activities such as shopping or walking approximately 3 blocks. Physical exam is remarkable only for mild sacroiliac tenderness.

What is the most likely diagnosis?

- ☐ Idiopathic BTP
- ☐ End-of-dose BTP

- ☐ Predictable incident BTP
- ☐ Unpredictable incident BTP

You recommend that she use a pelvic corset, take rests between her activities, and keep the activities as brief as possible. Which of the following would you choose to manage this patient's BTP?

- ☐ Tramadol
- ☐ Increasing the dose of the LAO agent
- ☐ A short-acting opioid in anticipation of the pain
- ☐ Switch to a different LAO of comparable or greater potency

Three months later, she reports recurring pain despite initial desired response following your appropriate management. What is your next step with this patient?

- ☐ Reassurance and wait to see if symptoms improve with more time
- ☐ Increasing the dose of the LAO agent
- ☐ Meditation and biofeedback classes
- ☐ Refer her to a pain specialist

This activity is supported by an independent educational grant from Cephalon.

References

[CLOSE WINDOW]

References

1. Bennett D, Burton A, Fishman S, et al. Consensus panel recommendations for the assessment and management of breakthrough pain. Part 1. Pharm Ther. 2005;30:296-301.
2. Fine PG, Busch MA. Characterization of breakthrough pain by hospice patients and their caregivers. J Pain Symptom Manage. 1998;16:179-183. [Abstract](#)
3. Portenoy RK, Bennett DS, Rauck R, et al. Prevalence and characteristics of breakthrough pain in opioid-treated patients with chronic noncancer pain. J Pain. 2006;7:583-591. [Abstract](#)
4. Hwang SS, Chang VT, Kasimis B. Cancer breakthrough pain characteristics and responses to treatment at a VA medical center. Pain. 2003;101:55-64. [Abstract](#)
5. Caraceni A, Portenoy RK. An international survey of cancer pain characteristics and syndromes. IASP Task Force on Cancer Pain. International Association for the Study of Pain. Pain. 1999;82:263-274. [Abstract](#)
6. Caraceni A, Martini C, Zecca E, et al. Breakthrough pain characteristics and syndromes in patients with cancer pain. An international survey. Palliat Med. 2004;18:177-183. [Abstract](#)
7. Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence and characteristics. Pain. 1990;41:273-281. [Abstract](#)
8. Gomez-Batiste X, Madrid F, Moreno F, et al. Breakthrough cancer pain: prevalence and characteristics in patients in Catalonia, Spain. J Pain Symptom Manage. 2002;24:45-52. [Abstract](#)
9. Portenoy RK, Payne D, Jacobsen P. Breakthrough pain: characteristics and impact in patients with cancer pain. Pain. 1999;81:129-134. [Abstract](#)
10. Banning A, Sjogren P, Henriksen H. Treatment outcome in a multidisciplinary cancer pain clinic. Pain. 1991;47:129-134. [Abstract](#)
11. Zepetella G, O'Doherty CA, Collins S. Prevalence and characteristics of breakthrough pain in cancer patients admitted to a hospice. J Pain Symptom Manage. 2000;20:87-92. [Abstract](#)
12. Bennett DS, Simon S, Brennan M, Shoemaker SA. Prevalence and characteristics of breakthrough pain in patients receiving opioids for chronic back pain in pain specialty clinics. J Opioid Manag. 2007;3:101-106. [Abstract](#)
13. Simon S, Bennett DS, Rauck R, Taylor D, Shoemaker S. Breakthrough pain in opioid-treated patients with neuropathic pain. J Opioid Manag. 2006;2:347-352. [Abstract](#)
14. Payne R. Recognition and diagnosis of breakthrough pain. Pain Med. 2007;8:S3-S7. [Abstract](#)
15. Hanks G, Portenoy RK, MacDonald N, Forbes K. Difficult pain problems. In: Doyle D, Hanks GWC, MacDonald N, eds. Oxford Textbook of Palliative Medicine, 2nd edition. New York: Oxford University Press; 1998:454-477.
16. Coluzzi PH. Cancer pain management: newer perspectives on opioids and episodic pain. Am J Hosp Palliat Care. 1998;15:13-

22. Abstract

17. Abraham JL. Assessing the patient in pain. In: Abraham JL, ed. *A Physician's Guide to Pain and Symptom Management in Cancer Patients*, 2nd edition. Baltimore, Md: Johns Hopkins University Press; 2005:107-147.
18. National Cancer Institute. Available at: <http://www.nci.nih.gov/cancertopics/pdq/supportivecare/pain/HealthProfessional>. Accessed November 22, 2007.
19. Svendsen KB, Andersen S, Arnason S, et al. Breakthrough pain in malignant and non-malignant diseases: a review of prevalence, characteristics and mechanisms. *Eur J Pain*. 2005;9:195-206. Abstract
20. Zeppetella G, O'Doherty CA, Collins S. Prevalence and characteristics of breakthrough pain in patients with non-malignant terminal disease admitted to a hospice. *Palliat Med*. 2001;15:243-246. Abstract
21. Zeppetella G. Breakthrough pain in cancer patients. *Adv Pain Manage*. 2007;1:5-11.
22. Taylor DR, Webster LR, Chun SY, et al. Impact of breakthrough pain on quality of life in patients with chronic, noncancer pain: patient perceptions and effect of treatment with oral transmucosal fentanyl citrate (OTFC, ACTIQ). *Pain Med*. 2007;8:281-288. Abstract
23. Ohayon MM, Schatzberg AF. Using chronic pain to predict depressive morbidity in the general population. *Arch Gen Psychiatry*. 2003;60:39-47. Abstract
24. Fortner BV, Okon TA, Portenoy RK. A survey of pain-related hospitalizations, emergency department visits, and physician office visits reported by cancer patients with and without history of breakthrough pain. *J Pain*. 2002;3:38-44. Abstract
25. Grant M, Ferrell BR, Rivera LM, Lee J. Unscheduled readmissions for uncontrolled symptoms. A health care challenge for nurses. *Nurs Clin North Am*. 1995;30:673-682. Abstract
26. Brennan F, Carr DB, Cousins M. Pain management: a fundamental human right. *Anesth Analg*. 2007;105:205-221. Abstract
27. Cleeland CS, Gonin R, Hatfield AK, et al. Pain and its treatment in outpatients with metastatic cancer. *N Engl J Med*. 1994;330:592-596. Abstract
28. Carr D, Goudas L, Balk E, Bloch R, Ioannidis J, Lau J. Evidence report on the treatment of pain in cancer patients. *J Natl Cancer Inst Monogr*. 2004:23-31.
29. Ward SE, Goldberg N, Miller-McCauley V, et al. Patient-related barriers to management of cancer pain. *Pain*. 1993;52:319-324. Abstract
30. American Pain Foundation. Pain notebook. Available at: <http://www.painfoundation.org/Publications/Notebook.pdf>. Accessed November 26, 2007.
31. de Wit R, van Dam F, Hanneman M, et al. Evaluation of the use of a pain diary in chronic cancer pain patients at home. *Pain*. 1999;79:89-99. Abstract
32. Maunsell E, Allard P, Dorval M, Labbe J. A brief pain diary for ambulatory patients with advanced cancer: acceptability and validity. *Cancer*. 2000;88:2387-2397. Abstract
33. Passik SD, Kirsh KL, Whitcomb L, et al. A new tool to assess and document pain outcomes in chronic pain patients receiving opioid therapy. *Clin Ther*. 2004;26:552-561. Abstract
34. McCarberg BH. The treatment of breakthrough pain. *Pain Med*. 2007;8:S8-S13. Abstract
35. Driver LC. Case studies in breakthrough pain. *Pain Med*. 2007;8:S14-S18. Abstract
36. Bennett D, Burton A, Fishman S, et al. Consensus panel recommendations for the assessment and management of breakthrough pain. Part 2. *Pharm Ther*. 2005;30:354-361.
37. Menefee LA, Monti DA. Nonpharmacologic and complementary approaches to cancer pain management. *J Am Osteopath Assoc*. 2005;105:S15-20. Abstract
38. Ferrell BR, Rhiner M, Ferrell BA. Development and implementation of a pain education program. *Cancer*. 1993;72:3426-3432. Abstract
39. Mercadante S, Radbruch L, Caraceni A, et al. Episodic (breakthrough) pain. Consensus conference of an expert working group of the European Association for Palliative Care. *Cancer*. 2002;94:832-839. Abstract
40. Guilherme Soares L, Chan VW. The rationale for a multimodal approach in the management of breakthrough cancer pain: a review. *Am J Hosp Palliat Med*. 2007;24:430-439.
41. Fisher K, Stiles C, Hagen NA. Characterization of the early pharmacodynamic profile of oral methadone for cancer-related breakthrough pain: a pilot study. *J Pain Symptom Manage*. 2004;28:619-625. Abstract
42. Zeppetella G. Opioids for cancer breakthrough pain: a pilot study reporting patient assessment of time to meaningful pain relief. *J Pain Symptom Manage*. 2008; [Epub ahead of print].
43. Portenoy RK, Payne R, Coluzzi P, et al. Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study. *Pain*. 1999;79:303-312. Abstract
44. Coluzzi PH, Schwartzberg L, Conroy JD, et al. Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). *Pain*. 2001;91:123-130. Abstract
45. Zeppetella G, Ribeiro MDC. Opioids for the management of breakthrough (episodic) pain in cancer patients. *Cochrane Database Syst Rev*. 2006;(1):CD004311.
46. Mystakidou K, Katsouda E, Parpa E, Tsiatas ML, Vlahos L. Oral transmucosal fentanyl citrate for the treatment of breakthrough pain in cancer patients: an overview of its pharmacological and clinical characteristics. *J Opioid Manag*. 2005;1:36-40. Abstract
47. Hanks GW, Nugent M, Higgs CM, Busch MA; OTFC Multicentre Study Group. Oral transmucosal fentanyl citrate in the management of breakthrough pain in cancer: an open, multicentre, dose-titration and long-term use study. *Palliat Med*. 2004;18:698-704. Abstract
48. Darwish M, Tempero K, Kirby M, Thompson J. Relative bioavailability of the fentanyl effervescent buccal tablet (FEBT) 1,080 pg versus oral transmucosal fentanyl citrate 1,600 pg and dose proportionality of FEBT 270 to 1,300 microg: a single-dose, randomized, open-label, three-period study in healthy adult volunteers. *Clin Ther*. 2006;28:715-724. Abstract
49. Slatkin NE, Xie F, Messina J, Segal TJ. Fentanyl buccal tablet for relief of breakthrough pain in opioid-tolerant patients with cancer-related chronic pain. *J Support Oncol*. 2007;5:327-334. Abstract
50. Darwish M, Kirby M, Robertson P Jr, Tracewell W, Jiang JG. Absolute and relative bioavailability of fentanyl buccal tablet and

- oral transmucosal fentanyl citrate. *J Clin Pharmacol*. 2007;47:343-350. [Abstract](#)
51. Darwish M, Kirby M, Jiang JG, Tracewell W, Robertson P Jr. Bioequivalence following buccal and sublingual placement of fentanyl buccal tablet 400 microg in healthy subjects. *Clin Drug Investig*. 2008;28:1-7. [Abstract](#)
52. Hagen NA, Fisher K, Stiles C. Sublingual methadone for the management of cancer-related breakthrough pain: a pilot study. *J Palliat Med*. 2007;10:331-337. [Abstract](#)
53. Osborne R, Joel S, Trew D, Slevin M. Morphine and metabolite behavior after different routes of morphine administration: demonstration of the importance of the active metabolite morphine-6-glucuronide. *Clin Pharmacol Ther*. 1990;47:12-19. [Abstract](#)
54. Weinberg DS, Inturrisi CE, Reidenberg B, et al. Sublingual absorption of selected opioid analgesics. *Clin Pharmacol Ther*. 1988;44:335-342. [Abstract](#)
55. Lennernas B, Hedner T, Holmberg M, Bredenberg S, Nystrom C, Lennernas H. Pharmacokinetics and tolerability of different doses of fentanyl following sublingual administration of a rapidly dissolving tablet to cancer patients: a new approach to treatment of incident pain. *Br J Clin Pharmacol*. 2005;59:249-253. [Abstract](#)
56. Lehmann KA. Recent developments in patient-controlled analgesia. *J Pain Symptom Manage*. 2005;29(5 suppl):S72-89.
57. Viscusi ER, Siccaldi M, Damaraju CV, Hewitt DJ, Kershaw P. The safety and efficacy of fentanyl iontophoretic transdermal system compared with morphine intravenous patient-controlled analgesia for postoperative pain management: an analysis of pooled data from three randomized, active-controlled clinical studies. *Anesth Analg*. 2007;105:1428-1436. [Abstract](#)
58. Farr SJ, Otulana BA. Pulmonary delivery of opioids as pain therapeutics. *Adv Drug Deliv Rev*. 2006;58:1076-1088. [Abstract](#)
59. Slatkin N. Analgesic efficacy of morphine delivered with the AERx mPMS for breakthrough cancer pain (open label cross-over). Program and abstracts of the 21st Annual Meeting of the American Pain Society; March 14-17, 2002; Baltimore, Maryland
60. Jekunen AP, Cotterill-Jones C, Dewlan P, et al. *J Clin Oncol*. 2006;24(18 suppl):8629.
61. Christie JM, Simmonds M, Patt R, et al. Dose-titration, multicenter study of oral transmucosal fentanyl citrate for the treatment of breakthrough pain in cancer patients using transdermal fentanyl for persistent pain. *J Clin Oncol*. 1998;16:3238-3245. [Abstract](#)
62. Portenoy RK, Taylor D, Messina J, Tremmel L. A randomized, placebo-controlled study of fentanyl buccal tablet for breakthrough pain in opioid-treated patients with cancer. *Clin J Pain*. 2006;22:805-811. [Abstract](#)

Authors and Disclosures

As an organization accredited by the ACCME, Medscape, LLC requires everyone who is in a position to control the content of an education activity to disclose all relevant financial relationships with any commercial interest. The ACCME defines "relevant financial relationships" as financial relationships in any amount, occurring within the past 12 months, including financial relationships of a spouse or life partner, that could create a conflict of interest.

Medscape, LLC encourages Authors to identify investigational products or off-label uses of products regulated by the US Food and Drug Administration, at first mention and where appropriate in the content.

Author

Neal E. Slatkin, MD

Professor, Department of Neurology; Director, Pain & Palliative Medicine, City of Hope National Medical Center, Duarte, California

Disclosure: Neal E. Slatkin, MD, had disclosed that he has served as a consultant to Biodelivery Sciences International, Cephalon, and Archimedes.

Michelle I. Rhiner, RN, MSN, NP

Director, Palliative Care Education; Department of Supportive Care, Pain & Palliative Medicine, City of Hope National Medical Center, Duarte, California

Disclosure: Michelle I. Rhiner, RN, MSN, NP, has disclosed that she has received grants for clinical research from Cephalon and BEMA (BDSI). Ms. Rhiner has also disclosed that she has served as an advisor or consultant to Cephalon.

Editor

Stephanie Kushner, PhD

Scientific Director, Medscape, LLC

Disclosure: Stephanie Kushner, PhD, has disclosed no relevant financial relationships.

Registration for CME credit, the post test and the evaluation must be completed online.

To access the activity Post Test and Evaluation link, please go to:

http://www.medscape.com/viewprogram/9080_index